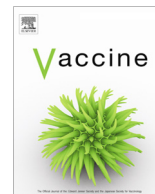




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Safety and immunogenicity of a novel 10-valent pneumococcal conjugate vaccine candidate in adults, toddlers, and infants in The Gambia—Results of a phase 1/2 randomized, double-blinded, controlled trial

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ABSTRACT

Background: A more affordable pneumococcal conjugate vaccine (PCV) that provides comparable protection to current PCVs is needed to ensure sustainable access in resource-limited settings. Serum Institute of India Pvt. Ltd.'s PCV candidate (SIPL-PCV) has the potential to meet this need as manufacturing efficiency has been optimized and the vaccine targets the most prevalent disease-causing serotypes in Africa and Asia. We report SIPL-PCV's safety, tolerability, and immunogenicity in adults, toddlers, and infants in The Gambia.

Methods: This phase 1/2, randomized, double-blind trial sequentially enrolled 34 PCV-naïve adults (18–40 years old), 112 PCV (Prevenar 13[®] [PCV13])–primed toddlers (12–15 months old), and 200 PCV-naïve infants (6–8 weeks old), who were randomized (1:1) to receive SIPL-PCV or a licensed comparator vaccine. Infants received three-doses of SIPL-PCV or PCV13 at 6, 10, and 14 weeks of age co-administered with routine Expanded Program on Immunization (EPI) vaccines. Reactogenicity was solicited through seven-days post-vaccination; unsolicited adverse events (AEs) were assessed throughout the study. The safety and immunogenicity of a matching booster at 10–14 months of age were evaluated in a subset of 96 infants. Immune responses were evaluated post-primary and pre- and post-booster vaccinations.

Results: Reactogenicity was primarily mild-to-moderate in severity. In infants, the most common solicited reactions were injection-site tenderness and fever, with no meaningful treatment-group differences. There were no serious or severe vaccine-related AEs and no meaningful trends in SAEs, vaccine-related AEs, or overall AEs. Infant post-primary seroresponse rates (IgG level ≥ 0.35 $\mu\text{g/mL}$) were $\geq 89\%$ for all serotypes except 6A (79%) in the SIPL-PCV group. IgG GMCs were >1 $\mu\text{g/mL}$ for all serotypes in both SIPL-PCV and PCV13 groups. Post-booster GMCs were comparable between groups.

Conclusion: SIPL-PCV was well-tolerated, had an acceptable safety profile, and was immunogenic for all vaccine serotypes. Results support the evaluation of SIPL-PCV in a phase 3 non-inferiority trial.

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1. Introduction

Streptococcus pneumoniae is the leading cause of severe pneumonia worldwide, a condition which, in 2015, caused nearly one million deaths in children under five years old [1]. Invasive pneu-

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mococcal disease (IPD), including sepsis and meningitis, also results in high childhood morbidity and mortality, particularly in low-resource settings [2,3].

Pneumococcal conjugate vaccines (PCVs) are highly effective at protecting children from IPD and their introduction has substantially reduced morbidity and mortality from pneumococcal disease in children, including in The Gambia where this study was undertaken [3–8]. Despite this, the burden of vaccine-preventable pneumococcal pneumonia and IPD remains high in many low-resource settings related to delayed PCV introduction and low coverage [2,3]. The high cost of PCVs makes them difficult for low- and middle-income countries (LMICs) to afford without considerable financial assistance, and places a high financial burden on countries graduating from support for vaccine purchase from Gavi, the Vaccine Alliance [9,10]. Increased access to safe, efficacious, and affordable PCVs could therefore substantially reduce pneumococcus-related childhood morbidity and mortality [9,11].

The 10-valent candidate PCV developed by Serum Institute of India Pvt. Ltd. (SIPL), SIPL-PCV, incorporates the most prevalent IPD-causing serotypes prior to PCV introduction in Africa, Asia, and Latin America (1, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F, and 23F). Thus, the vaccine offers comparable serotype coverage to licensed PCVs in these settings [12]. Furthermore, SIPL has lowered SIPL-PCV's manufacturing costs by optimizing three critical components of the manufacturing process: carrier protein production, polysaccharide production, and conjugation efficiency. Therefore, if SIPL-PCV is found to be safe and immunogenic, it will be provided at a considerably lower price than currently licensed PCVs.

This phase 1/2, age de-escalation trial evaluated the safety, tolerability (primary objectives), and immunogenicity (secondary objectives) of SIPL-PCV compared to the licensed 23-valent pneumococcal polysaccharide vaccine (Pneumovax23®, Merck® [PPSV23]) in adults and compared to the 13-valent PCV (Prevnar13®, Pfizer® [PCV13]) in toddlers and infants. Adults and toddlers received a single dose of either SIPL-PCV or comparator vaccine while infants received three-doses of either SIPL-PCV or PCV13 at 6, 10, and 14 weeks old. In infants, PCV was co-administered with the routine Expanded Program on Immunization (EPI) vaccines. The immune responses to components of co-administered pentavalent vaccine (diphtheria, tetanus, whole-cell pertussis, hepatitis B, and *Haemophilus influenzae* type b [DTwP-HepB-Hib]), and the safety, tolerability, and immunogenicity of a booster dose of SIPL-PCV given to a subset of infants between 10 and 14 months old were also investigated.

2. Methods

2.1. Study design and participants

This was a phase 1/2, parallel-group, randomized, double-blind, age de-escalation trial conducted by MRC Unit The Gambia—part of the London School of Hygiene and Tropical Medicine—in clinical trial facilities in the peri-urban Western region of The Gambia. Sequential cohorts of 34 PCV-naïve adults (18–40 years old), 112 PCV13-vaccinated toddlers (12–15 months old), and 200 PCV-naïve infants (6–8 weeks old) were enrolled starting in January 2015. The last subject completed post-booster follow-up in November 2016. All toddlers had previously received three-doses of PCV13 according to the two-, three-, and four-month EPI schedule in The Gambia. All subjects/parents provided written informed consent prior to the conduct of any trial-related procedures and were deemed healthy based on defined eligibility criteria (Table S1). An unblinded data and safety monitoring board reviewed safety data before vaccination of the next descending age cohort began. To evaluate immune persistence and the

response to booster vaccination post-priming, the protocol was amended to include a matching dose of either SIPL-PCV or PCV13 to be given at ≥ 10 months old to booster-eligible infant subjects whose parent provided separate consent.

Adults were randomized 1:1 (stratified by sex) to receive a single dose of either SIPL-PCV or PPSV23, while toddlers and infants were randomized 1:1 to receive either SIPL-PCV or PCV13 (single booster dose for toddlers, three-dose primary series for infants). Randomization sequences were generated using permuted blocks with randomly selected block sizes by an independent biostatistician implementing a validated SAS® macro. Vaccine assignment was indicated in individual, sequentially-numbered, sealed, opaque, tamper-evident envelopes. Once subject eligibility was confirmed, randomization was undertaken by unblinded nurses using the next envelope in sequence. The same unblinded nurses prepared and administered all vaccinations in the study but were not involved in any other subject-related procedures or endpoint assessments. During the primary study, subjects, parents, and all study staff except the unblinded nurses were blinded to treatment assignment. The infant booster phase (added after study unblinding) was single-blinded. The investigator and study clinicians were unblinded to group assignment but all other site staff, laboratory personnel, and subjects' parents remained blinded.

Adults and toddlers underwent four clinic visits (screening, vaccination, and follow-up at 7 days [d] and 28d post-vaccination). Infants underwent up to 11 clinic visits (primary phase: screening, three vaccination visits 28d apart, each with follow-up visit 7d post-vaccination, plus two follow-up visits 28d and 84d after the final vaccination; booster phase: booster vaccination visit, follow-up visit 28d post-booster) (Fig. 1).

Following each vaccination, trained field workers conducted daily home visits to solicit injection-site and systemic reactogenicity. Participants were also asked to contact the study team with any health-related concerns at any time during the study and, under such circumstances, were seen by a study clinician who provided treatment or referral if necessary, and recorded all adverse events (AEs).

A single 0.5 mL dose of SIPL-PCV contains 2 µg of polysaccharide for serotypes 1, 5, 9V, 14, 19A, 19F, 23F, 7F, and 6A, and 4 µg for serotype 6B, each individually conjugated to the diphtheria toxoid-derived recombinant Cross-Reactive-Material 197 (CRM₁₉₇), with 0.125 mg per dose of aluminum as aluminum phosphate. Lot 209E3001 was used throughout. PPSV23 and PCV13 composition has been described previously [13,14]. All study vaccines were administered intramuscularly using a 23G 25 mm needle into the mid-deltoid of the subject's non-dominant arm in adults and the mid-thigh in toddlers and infants. DTwP-HepB-Hib (SIPL), bivalent oral poliovirus vaccine (SIPL), and oral rotavirus vaccine (Rotateq®, MSD Vaccines) were co-administered with all primary doses, and inactivated poliovirus vaccine (SIPL) was co-administered with the third dose according to The Gambian EPI schedule.

The study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki, and registered with ClinicalTrials.gov (NCT02308540). The Gambia Government/MRC Joint Ethics Committee, Medicines Board of The Gambia Government, and Western Institutional Review Board approved the study protocol, amendments, and informed consent forms.

2.2. Assessments

Blood samples were collected pre-vaccination and 28d post-vaccination for adults and toddlers, and pre-vaccination and 28d post third vaccination for infants. Infants receiving a booster were bled pre-booster and 28d post-booster. Injection-site and systemic reactogenicity was solicited in clinic one hour (h) (30 min post-

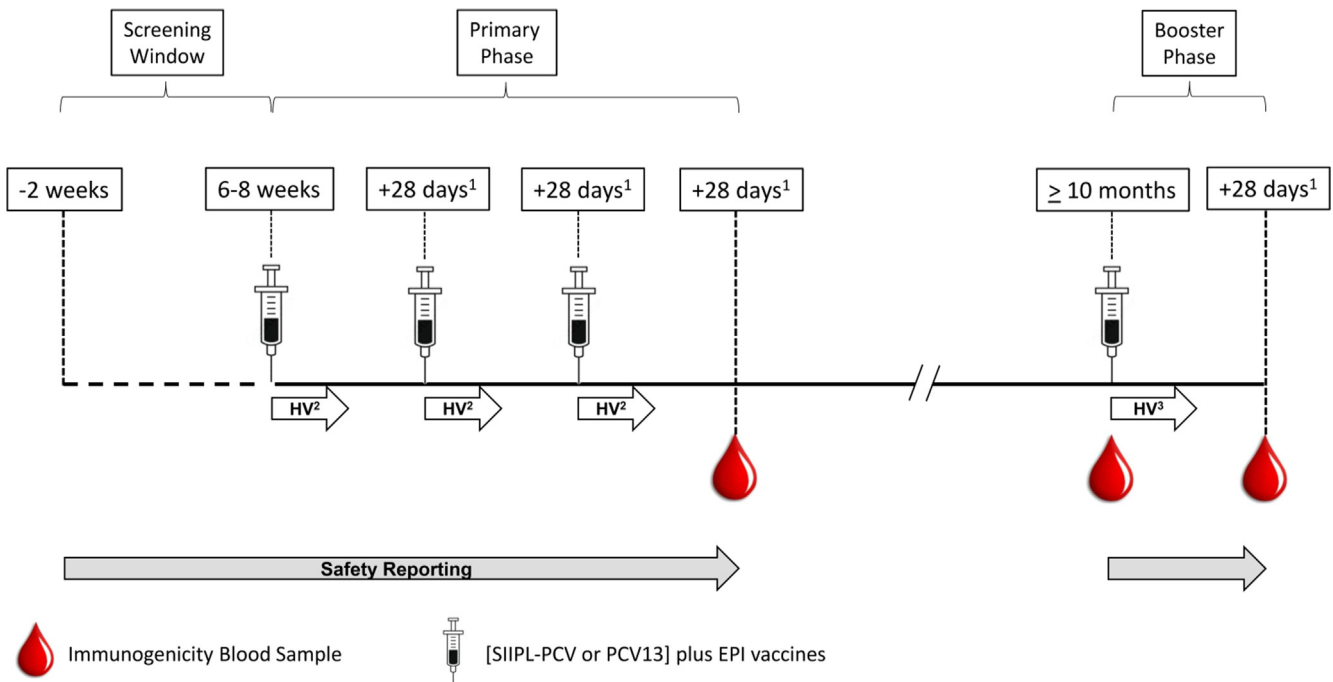


Fig. 1. Study design for infant cohort. Infants were vaccinated at between 6 and 8 weeks of age. Screening began from up to 2 weeks before this.¹Visits took place at 28–42 day intervals; ²Solicited injection-site and systemic reactogenicity collected through post-vaccination day 1 to day 6 home visits (HV) plus a day 7 clinic visit; ³Solicited injection-site and systemic reactogenicity collected through post-vaccination day 1 to day 6 home visits (HV); Safety reporting of unsolicited adverse events.

booster) and daily for 7d post-vaccination (6d post-booster) and was severity-graded (one to four) per protocol definitions. Any ongoing reactogenicity at the end of the follow-up period (e.g., persistent injection-site swelling) was reported as an unsolicited AE and followed up accordingly. Biochemical and hematological laboratory examinations were undertaken at screening in all cohorts and 7d post-vaccination in adults and toddlers. Unsolicited AEs were recorded from consent through 28d (adult and toddler cohorts) or 84d (infant primary phase) following vaccination. For infants in the booster phase, AEs were additionally recorded from the booster visit through 28d post-booster. AEs were categorized using MedDRA version 17.1 and severity graded from one (mild) to five (resulted in death) per protocol definitions. Vaccine-relatedness of systemic reactogenicity and treatment-emergent AEs (TEAEs) was evaluated by site clinicians. Clinical laboratory evaluations and vital signs were toxicity-graded per protocol definitions and assessed for clinical significance by a study clinician.

Immunogenicity was evaluated by the World Health Organization (WHO) Pneumococcal Serology Reference Laboratory, University College London, United Kingdom, using a validated enzyme-linked immunosorbent assay to quantify pneumococcal serotype-specific immunoglobulin G (IgG) concentrations, and a four-fold multiplexed opsonophagocytic assay (OPA) to quantify functional immune responses [15,16]. Seroreponse was defined as a serum IgG level $\geq 0.35 \mu\text{g/mL}$, a threshold associated with protection against IPD in infants; seroreponse based on the functional assay was defined as a reciprocal OPA titer ≥ 8 [17–19]. IgG concentrations were measured in the infant cohort for each component of the co-administered DTwP–HepB–Hib vaccine at Public Health England laboratories, United Kingdom. Seroprotection thresholds for all pentavalent components except pertussis antigens were predefined.

2.3. Statistical analysis

The analysis of this phase 1/2 study was descriptive. No hypothesis testing was planned. The sample size of each cohort was cho-

sen to provide sufficient data to support age-de-escalation and, subsequently, safety and immunogenicity data to support decisions regarding further evaluation of SIIP-PCV in phase 3 trials.

The sample size of 100 infants per group provided a $\geq 90\%$ chance of observing an AE with a 2.3% occurrence rate. If no AE occurred, the upper limit of the one-sided 95% confidence interval (CI) for the occurrence rate was 3.0%. The same sample size provided $>99\%$ power to detect a two-fold difference in geometric mean concentration (GMC) between groups and $>80\%$ power to detect a 10% lower seroreponse rate following SIIP-PCV assuming a 98% seroreponse following PCV13. Although not tested in this study, these criteria are relevant because they reflect the margins of immunologic non-inferiority used in previous PCV licensure trials [20,21].

Safety endpoints were injection-site and systemic reactogenicity and TEAEs and were evaluated descriptively.

Immunogenicity endpoints were GMCs or geometric mean titers (GMTs); geometric mean fold-rise (GMFR), where fold-rise was calculated as a subject's later measurement divided by their earlier measurement; and seroreponse rates. Treatment groups were compared using GMC ratio, GMT ratio or GMFR ratio (SIIP-PCV/comparator), and difference in seroreponse rates (SIIP-PCV minus comparator). In the infant cohort, a booster response was defined by comparing the GMC 28d post-booster with the GMC 28d post-primary series. The GMC post-booster was also compared with the GMC pre-booster in the toddler and infant cohorts.

The CIs around proportions and differences in proportions were calculated using exact methods (exact binomial and unconditional exact method [22], respectively). The CIs around GMCs, etc. were constructed using t-tests assuming log-normality or, where this assumption was not met, from bootstrap resampling (10,000 replicates) [23,24].

Subjects who did not complete the study contributed to analyses as available. Immunogenicity assays reported as below the limit of quantification (LOQ) were assigned a value of one-half the LOQ; otherwise, no imputation was conducted. Since $>80\%$ of HepB antibody concentrations were reported as $>1000 \text{ mIU/mL}$,

the percent exceeding the seroresponse threshold was calculated but GMCs were not.

3. Results

3.1. Disposition and demographics

All cohorts met recruitment targets and all adults (Fig. 2A) and toddlers (Fig. 2B) completed the study *per protocol*. One infant in the PCV13 group withdrew from the study; therefore, 199 of 200 (99.5%) infants completed the study *per protocol* (Fig. 2C). A total of 96 infants (49 SIIPL-PCV, 47 PCV13) received a booster dose of study vaccine and contributed to the booster analysis (Fig. 2D).

Treatment groups in all cohorts were well-balanced with respect to age, sex, weight, and height/length (Table 1; adult and toddler data not shown).

3.2. Safety

3.2.1. Adults

All solicited injection-site and systemic reactogenicity in adults was mild and resolved within 24–48 h, with no meaningful differences between treatment groups (data not shown).

Four (23.5%) and 10 (58.8%) adults in the SIIPL-PCV and PPSV23 groups, respectively, had at least one TEAE, most commonly a gastrointestinal disorder (11.8% and 35.3% of adults in each group respectively), all of which were mild or moderate in severity. Five vaccine-related TEAEs occurred in adults (one in the SIIPL-PCV group [pain in the axilla] and four in the PPSV23 group), all of which were mild. No SAEs occurred in adults.

3.2.2. Toddlers

Injection-site tenderness was elicited in comparable proportions between groups (Table S2). Injection-site swelling occurred in 10.7% of those receiving SIIPL-PCV compared to 1.8% of those receiving PCV13. All injection-site reactions were mild or moderate, and generally resolved within 24–48 h. Drowsiness was reported in 10.7% of toddlers who received SIIPL-PCV and was not reported following PCV13 administration. There were no other notable differences in systemic reactogenicity between groups. Systemic reactogenicity was mild to moderate, except for three events of severe ($>39^{\circ}\text{C}$ – 40°C) fever, two of which occurred following PCV13 and one following SIIPL-PCV.

The proportion of toddlers with at least one TEAE was similar between groups. The most common TEAEs in toddlers were infections (44.6% SIIPL-PCV, 50.0% PCV13), particularly upper respiratory tract infections (URTIs), and gastrointestinal disorders (16.1% SIIPL-PCV, 10.7% PCV13), including diarrhea (Table S2).

Two toddlers in the SIIPL-PCV group and one in the PCV13 group had a mild or moderate vaccine-related TEAE (mild diarrhea and moderate rash following SIIPL-PCV). Four severe TEAEs occurred, including two cases of microcytic anemia in the SIIPL-PCV group deemed unrelated to vaccination. Two severe SAEs occurred—one (gastroenteritis) in the SIIPL-PCV group and one (pneumonia) in the PCV13 group, both of which were deemed unrelated to vaccination and resolved without sequelae.

3.2.3. Infants

In the infant cohort, no severe solicited injection-site reactions were reported. One severe fever occurred in each group. One episode of severe cutaneous rash and one episode of severe irritability were also reported in the SIIPL-PCV group during the primary phase of the trial. In the booster phase, two of 49 infants in the SIIPL-PCV group (4.1%) and one of 47 infants in the PCV13 group (2.1%) had a severe fever. While the rates of injection-site and sys-

temic reactogenicity after each of the three vaccinations in infants were somewhat variable, no trends were apparent following either SIIPL-PCV or PCV13 (Table 2).

Nearly all infants had at least one TEAE (97.0% in the SIIPL-PCV group versus 96.0% in the PCV13 group). The most common TEAEs in infants were injection-site reactions related to co-administered DTwP-HepB-Hib vaccine, and URTIs (Table 3). Ten infants had a study vaccine-related TEAE (two in the SIIPL-PCV group and eight in the PCV13 group)—primarily persistent injection-site swelling (two and seven infants, respectively).

Six infants in the SIIPL-PCV group and two infants in the PCV13 group had an SAE. The only SAE reported in more than two infants was bronchiolitis (three infants [four events] in the SIIPL-PCV group and one infant [one event] in the PCV13 group). All SAEs were deemed unrelated to vaccination and resolved without sequelae.

The only severe TEAEs reported in more than one infant were two bronchiolitis events in the SIIPL-PCV infant group. No concerning trends were observed in the frequency of any grade of TEAE.

3.2.4. Additional safety assessments

No noteworthy trends from baseline were observed in vital signs, physical examination findings or post-vaccination laboratory examinations.

3.3. Immunogenicity results

3.3.1. Adults

In adults, the serotype-specific IgG GMC ranged from 3.56 $\mu\text{g}/\text{mL}$ (95% CI: 1.89–6.72) for serotype 5 to 48.23 $\mu\text{g}/\text{mL}$ (95% CI: 28.87–80.59) for serotype 14 following SIIPL-PCV, and from 3.64 $\mu\text{g}/\text{mL}$ (95% CI: 2.41–5.52) for serotype 6A to 44.78 $\mu\text{g}/\text{mL}$ (95% CI: 31.04–64.59) for serotype 14 following PPSV23. The GMCs were higher following SIIPL-PCV for serotypes 6A and 6B (GMC ratio 4.69 [95% CI: 2.16–10.20] and 2.22 [95% CI: 1.02–4.84], respectively) and were higher following PPSV23 for serotypes 1 and 9V (GMC ratio 0.31 [95% CI: 0.15–0.64] and 0.56 [95% CI: 0.34–0.95], respectively). The responses to the remaining six serotypes were comparable between groups (Table S3).

OPA GMTs were also higher for serotypes 6A and 6B following SIIPL-PCV (GMT ratio 3.48 [95% CI: 1.71–6.37] and 3.15 [95% CI: 1.76–5.61], respectively) and for serotype 1 alone following PPSV23 (GMT ratio 0.22 [95% CI: 0.07–0.99]) (Table S3).

3.3.2. Toddlers

In PCV13-primed toddlers, the serotype-specific IgG GMCs after the booster dose of either SIIPL-PCV or PCV13 were comparable (Table 4). The GMCs ranged from 2.30 $\mu\text{g}/\text{mL}$ (95% CI: 1.57–3.72) for serotype 5 to 15.77 $\mu\text{g}/\text{mL}$ (95% CI: 11.51–23.96) for serotype 6B following SIIPL-PCV and from 3.35 $\mu\text{g}/\text{mL}$ (95% CI: 2.46–5.35) to 19.16 $\mu\text{g}/\text{mL}$ (95% CI: 14.98–30.46) for the same serotypes, respectively, following PCV13.

There was a substantial booster response for all serotypes in both groups (Table 4). The GMFRs following SIIPL-PCV ranged from 3.82 (95% CI: 2.48–7.34) for serotype 5 to 9.91 (95% CI: 5.58–22.32) for serotype 6A. The GMFRs following PCV13 ranged from 3.35 (95% CI: 2.26–5.56) for serotype 14 to 24.17 (95% CI: 17.04–38.35) for serotype 19A. The GMFR ratios ranged from 0.33 (95% CI: 0.15–0.77) for serotype 19A to 1.50 (95% CI: 0.78–2.78) for serotype 14 and were higher for serotypes 5, 9V, and 19A following PCV13 than following SIIPL-PCV.

The OPA GMTs following the booster vaccination in toddlers were broadly comparable (Table 4). GMT ratios ranged from 0.78 (95% CI: 0.32–1.69) for serotype 9V to 3.21 (95% CI: 1.36–7.44) for serotype 14. The response to serotype 14 alone was higher in the SIIPL-PCV group.

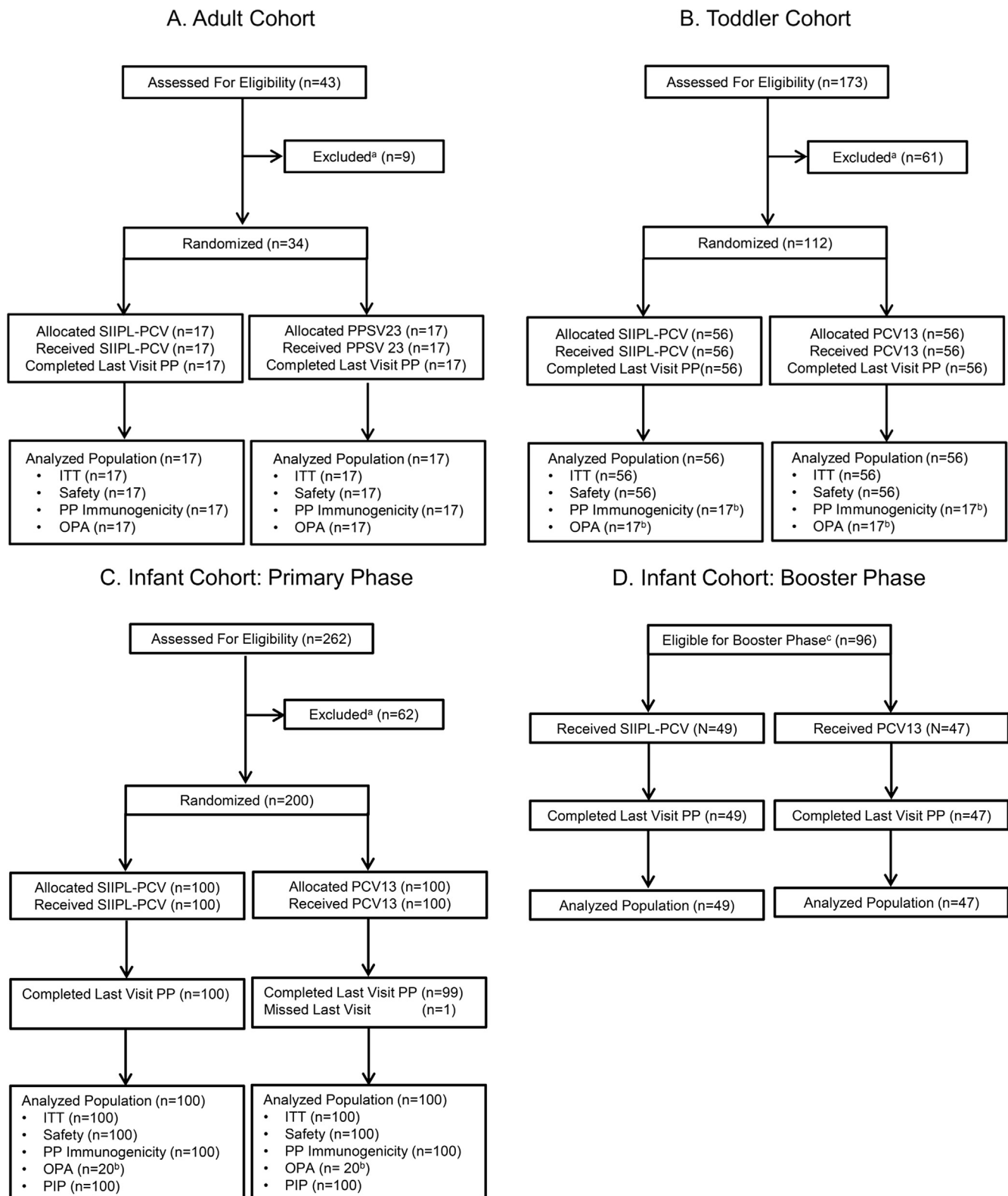


Fig. 2. Flow of subjects. ^aComprises screen failures and eligible subjects screened when cohort recruitment was completed; ^bAssays undertaken on a randomly selected subset of subjects; ^cInfants were eligible if the parent provided additional informed consent and the subject had not already received an additional booster dose of PCV13; ITT—Intention to treat; PP—Per Protocol; PP Immunogenicity—number of subjects included in the serotype-specific pneumococcal IgG analysis; OPA—number of subjects included in the OPA analysis; PIP—number of subjects included in the pentavalent interference population.

3.3.3. Infants

3.3.3.1. Primary series responses. In infants, the point estimates for seroresponse rates were >90% for all serotypes following the

three-dose primary series of PCV13 and were >90%, and comparable to PCV13 responses, for 8 of 10 serotypes following the same SIIPL-PCV schedule (Table 5). The seroresponse rate was 79.0%

Table 1
Demographic characteristics of infants.

Characteristic	Primary Phase		Booster Phase	
	SIIP-PCV N = 100	PCV13 N = 100	SIIP-PCV N = 49	PCV13 N = 47
Sex, n (%)				
Male	48 (48.0)	51 (51.0)	29 (59.2)	27 (57.4)
Mean (SD) age at vaccination 1 (days)	47.2 (4.0)	47.3 (3.8)		
Mean (SD) age at booster vaccination (months)			11.4 (0.8)	11.5 (0.9)
Mean (SD) weight at vaccination 1 (kg)	4.7 (0.5)	4.7 (0.6)		
Mean (SD) length at vaccination 1 (cm)	55.3 (1.8)	55.5 (2.0)		
Race, n (%)				
African	100 (100.0)	99 (99.0)	49 (100.0)	47 (100.0)
Other	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Ethnic group, n (%)				
Mandinka	42 (42.0)	55 (55.0)	23 (46.9)	28 (59.6)
Wolof	18 (18.0)	10 (10.0)	9 (18.4)	2 (4.3)
Fula	12 (12.0)	10 (10.0)	6 (12.2)	5 (10.6)
Jola	12 (12.0)	12 (12.0)	5 (10.2)	3 (6.4)
Serahule	5 (5.0)	3 (3.0)	1 (2.0)	3 (6.4)
Serere	8 (8.0)	5 (5.0)	5 (10.2)	5 (10.6)
Manjago	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Other	3 (3.0)	4 (4.0)	0 (0.0)	1 (2.1)

SD—standard deviation; n (%)—number (percentage) of participants in a given category.

Table 2
Most common solicited reactogenicity events within 7 days of vaccination in the infant primary and booster phases.

Reactogenicity Event	Primary Phase						Booster Phase	
	Vaccination 1		Vaccination 2		Vaccination 3		Booster Dose ^a	
	SIIP-PCV N = 100 n (%)	PCV13 N = 100 n (%)	SIIP-PCV N = 100 n (%)	PCV13 N = 100 n (%)	SIIP-PCV N = 100 n (%)	PCV13 N = 100 n (%)	SIIP-PCV N = 49 n (%)	PCV13 N = 47 n (%)
<i>Local</i>								
Tenderness at injection site	19 (19)	17 (17)	20 (20)	27 (27)	21 (21)	21 (21)	9 (18.3)	11 (23.4)
Induration/swelling at injection site	4 (4)	10 (10)	8 (8)	18 (18)	13 (13)	14 (14)	6 (12.2)	4 (8.5)
<i>Systemic</i>								
Temperature (≥ 37.5 °C)	40 (40)	41 (41)	18 (18)	20 (20)	20 (20)	20 (20)	6 (12.2)	6 (12.7)
Irritability	37 (37)	31 (31)	40 (40)	33 (33)	37 (37)	41 (41)	5 (10.2)	7 (14.9)
Decreased appetite	10 (10)	1 (1)	10 (10)	8 (8)	7 (7)	11 (11)	2 (4.1)	5 (10.6)

n (%)—number (percentage); Number (percent) of subjects with grade ≥ 1 reactogenicity event during observation period.^a 6 days follow-up.**Table 3**
Most common ($\geq 5\%$ of subjects in any treatment group) treatment-emergent adverse events (TEAEs) in infant cohort, primary series.

Preferred Term ^b	SIIP-PCV N = 100 n ^a (%)	PCV13 N = 100 n ^a (%)
Subjects with at least 1 TEAE	97 (97%)	96 (96%)
Total TEAEs	414	356
● Upper respiratory tract infection	64 (64.0)	48 (48.0)
● Pentavalent vaccination site local reaction ^c	66 (66.0)	65 (65.0)
● Tinea infection	31 (31.0)	21 (21.0)
● Diarrhea	29 (29.0)	19 (19.0)
● Conjunctivitis	27 (27.0)	19 (19.0)
● Nasopharyngitis	19 (19.0)	17 (17.0)
● Gastroenteritis	13 (13.0)	10 (10.0)
● Cough	12 (12.0)	7 (7.0)

n (%)—number (percentage); AE—adverse event.

^a n reflects number of subjects in group with at least one event.^b TEAE coded using MedDRA version 17.1.^c Swelling, tenderness, erythema.

(95% CI: 69.7–86.5) against serotype 6A and was 89.0% (95% CI: 81.2–94.4) against serotype 6B following SIIP-PCV. These rates were lower than the responses to the same serotypes induced by

PCV13 (6A: –12.0% [95% CI: –21.9–2.0]; 6B: –7.9% [95% CI: –15.8–0.5]).

The point estimates for the serotype-specific IgG GMCs after the primary series were above 1 $\mu\text{g/mL}$ for all serotypes following both vaccines. The GMCs ranged from 1.02 $\mu\text{g/mL}$ (95% CI: 0.79–1.32) for serotype 6A to 4.96 $\mu\text{g/mL}$ (95% CI: 4.06–6.07) for serotype 14 following SIIP-PCV, and from 1.74 $\mu\text{g/mL}$ (95% CI: 1.49–2.03) for serotype 5 to 5.38 $\mu\text{g/mL}$ (95% CI: 4.68–6.19) for serotype 19F following PCV13. The GMC were higher following PCV13 for seven (6A, 6B, 7F, 9V, 19A, 19F, and 23F) of the 10 serotypes (Table 5).

Based on OPA titers, between 93.8% (95% CI: 69.8–99.8) and 100% of infants seroresponded following SIIP-PCV compared to between 84.6% (95% CI: 54.6–98.1) and 100% following PCV13. In both groups, the seroresponse rates based on OPA titers were lowest against serotype 1 but the responses between groups were comparable (Table 5).

The serotype-specific OPA GMTs following the primary series were comparable for the two vaccines for six (1, 5, 6B, 14, 19F, and 23F) of 10 serotypes. The responses were lower for the four remaining serotypes following SIIP-PCV than following PCV13 administration (Table 5).

Table 4

Pneumococcal serotype-specific IgG GMCs, GMFR (pre-vaccination to post-vaccination), GMFR ratios and OPA GMTs after a single dose of either SIIP-PCV or PCV13 in the toddler per protocol immunogenicity population.

	IgG GMC						OPA GMT		
	SIIP-PCV N = 17 ^a GMC (95% CI) ^b	PCV13 N = 17 ^a GMC (95% CI) ^b	SIIP-PCV/ PCV13 GMC ratio (95% CI) ^b p-value	SIIP-PCV N = 17 ^a GMFR (95% CI) ^b	PCV13 N = 17 ^a GMFR (95% CI) ^b	SIIP-PCV/ PCV13 GMFR Ratio (95% CI) ^b p-value	SIIP-PCV N = 17 ^a GMT (95% CI) ^b	PCV13 N = 17 ^a GMT (95% CI) ^b	SIIP-PCV/ PCV13 GMT ratio (95% CI) ^b p-value
1	4.59 (3.90, 5.87)	6.09 (4.51, 10.75)	0.75 (0.51, 1.46) 0.265	5.99 (3.60, 10.95)	6.59 (4.78, 12.25)	0.91 (0.44, 1.89) 0.795	436.31 (348.89, 607.71)	438.14 (231.14, 946.46)	1.00 (0.56, 3.30) 0.992
5	2.30 (1.57, 3.72)	3.35 (2.46, 5.35)	0.69 (0.41, 1.31) 0.206	3.82 (2.48, 7.34)	8.00 (6.45, 12.86)	0.48 (0.28, 0.99) 0.023	1358.22 (885.29, 2222.71)	1148.43 (879.86, 1816.25)	1.18 (0.69, 2.23) 0.576
6A	13.33 (9.62, 22.49)	15.83 (11.64, 26.80)	0.84 (0.51, 1.69) 0.566	9.91 (5.58, 22.32)	12.31 (9.17, 21.85)	0.80 (0.38, 1.99) 0.604	19371.45 (11518.40, 37805.99)	12001.09 (7558.53, 23870.11)	1.61 (0.77, 3.94) 0.247
6B	15.77 (11.51, 23.96)	19.16 (14.98, 30.46)	0.82 (0.53, 1.43) 0.446	7.79 (4.56, 16.25)	9.82 (7.74, 15.98)	0.79 (0.41, 1.77) 0.536	8768.08 (4960.46, 13752.15)	7066.76 (4083.54, 13133.54)	1.24 (0.55, 2.63) 0.587
7F	9.17 (7.42, 12.12)	12.35 (8.83, 19.74)	0.74 (0.48, 1.23) 0.219	6.16 (4.38, 10.66)	8.44 (6.38, 14.79)	0.73 (0.43, 1.46) 0.316	10723.98 (6679.71, 18430.03)	12737.21 (7378.18, 19488.47)	0.84 (0.44, 1.76) 0.628
9V	2.35 (1.57, 3.45)	3.90 (2.58, 6.31)	0.60 (0.34, 1.14) 0.097	4.43 (3.05, 7.44)	9.58 (7.32, 16.31)	0.46 (0.27, 0.91) 0.012	3770.19 (1773.95, 7008.61)	4862.30 (2879.67, 7466.32)	0.78 (0.32, 1.69) 0.546
14	14.55 (8.23, 21.52)	8.28 (6.19, 13.82)	1.76 (0.91, 2.98) 0.071	5.04 (3.28, 7.91)	3.35 (2.26, 5.56)	1.50 (0.78, 2.78) 0.208	8213.23 (3981.89, 15174.75)	2557.27 (1472.91, 4197.18)	3.21 (1.36, 7.44) 0.007
19A	9.76 (6.71, 12.62)	13.68 (6.06, 22.64)	0.71 (0.38, 1.56) 0.344	7.89 (3.98, 16.83)	24.17 (17.04, 38.35)	0.33 (0.15, 0.77) 0.008	1789.98 (512.04, 3884.58)	3780.56 (2172.11, 6633.20)	0.47 (0.12, 1.18) 0.184
19F	9.75 (7.36, 12.75)	12.87 (8.46, 22.39)	0.76 (0.44, 1.32) 0.328	5.73 (2.92, 15.98)	13.26 (8.51, 23.50)	0.43 (0.19, 1.29) 0.085	3036.60 (2016.57, 5666.12)	3371.52 (2038.70, 6441.92)	0.90 (0.44, 1.99) 0.787
23F	6.84 (4.28, 10.54)	10.49 (7.70, 19.64)	0.65 (0.35, 1.25) 0.204	9.67 (5.56, 18.98)	16.54 (11.80, 30.76)	0.58 (0.28, 1.30) 0.173	12415.92 (7356.56, 20760.08)	10517.81 (5019.59, 21439.57)	1.18 (0.53, 3.31) 0.716

IgG GMC – Immunoglobulin G geometric mean concentration; GMFR–geometric mean fold rise; OPA GMT – Opsonophagocytic assay titer geometric mean titer; CI – confidence interval.

^a Assays were conducted on a randomly selected subset.

^b 95% CIs estimated from bootstrap resampling.

3.3.3.2. Booster responses. Prior to the booster vaccination, GMCs were higher in the PCV13 group for serotypes 5, 7F, 14, and 19A and higher in the SIIP-PCV group for serotype 6B, reflecting differences in the kinetics of immune response between groups for certain serotypes (Table S4 and Fig. 3).

A substantial booster response was observed for all serotypes following PCV13 and for all serotypes except serotype 5 following SIIP-PCV (Table 6). Comparing GMCs post-booster with GMCs post-primary immunization, the GMC ratios ranged from 1.13 (95% CI: 0.87–1.44) for serotype 5 to 9.03 (95% CI: 5.92–13.79) for serotype 6A following SIIP-PCV and from 1.46 (95% CI: 1.12–1.89) for serotype 9V to 7.75 (95% CI: 5.49–10.94) for serotype 6A following PCV13. The magnitude of the booster response was greater for five serotypes (1, 6B, 9V, 19A, and 23F) following SIIP-PCV and for serotype 5 following PCV13 (Table 6). Only the GMC against serotypes 19A and 19F remained higher in the PCV13 group than in the SIIP-PCV group following the booster immunization (GMCR 19A: 0.44 [0.27 – 0.72]; 19F 0.65 [0.43 – 0.99]). Comparing GMCs immediately pre-booster with those post-booster showed a robust response for all serotypes following both vaccines (Table S5).

3.3.3.3. Responses to co-administered EPI vaccines. All infants had IgG concentrations above the defined seroprotective thresholds for tetanus, diphtheria, and HepB whether the three routine doses of DTWP-HepB-Hib vaccine were co-administered with SIIP-PCV or PCV13. A single infant was below the protective threshold for

Hib following co-administration with PCV13. No meaningful differences were observed in the GMC to any of the three pertussis antigens, tetanus toxoid, diphtheria toxoid, or Hib between groups (Table S6). As such, nothing was observed to indicate differential interference with responses to pentavalent vaccine components between SIIP-PCV and PCV13.

4. Discussion

This phase 1/2 trial provides safety, tolerability, and immunogenicity data on SIIP-PCV—a novel 10-valent PCV that contains serotypes chosen to maximize coverage against pneumococcal disease in LMICs. It also provides preliminary data to support the co-administration of SIIP-PCV with primary EPI vaccines. The study was completed as planned, with age de-escalation from adults to toddlers and from toddlers to infants dependent on an independent review of safety data from the preceding cohort.

SIIP-PCV was well-tolerated in all age cohorts, including when co-administered with EPI vaccines in infants. No noteworthy safety signals were identified. The rates of injection-site and systemic reactogenicity following SIIP-PCV were broadly comparable to those following the licensed comparator vaccines (PPSV23 in adults, PCV13 in toddlers and infants) and were consistent with rates previously reported in trials of the licensed PCVs in infants, including in The Gambia [21,25–27]. Where numerical treatment-group differences were apparent, they are likely to

Table 5

Pneumococcal serotype-specific IgG seroresponse rates, IgG GMCs, OPA seroresponse rates, OPA GMTs and treatment group differences four weeks after the third primary dose of either SIIP-PCV or PCV13 in the infant *per protocol* immunogenicity population.

	IgG GMC						OPA GMT ^a					
	SIIP-PCV N = 100		PCV13 N = 100		SIIP-PCV vs. PCV13		SIIP-PCV N = 20		PCV13 N = 20		SIIP-PCV vs. PCV13	
	% ≥0.35 μg/mL (95% CI)	GMC (95% CI)	% ≥0.35 μg/mL (95% CI)	GMC (95% CI)	% diff ^b (95% CI) p-value	GMC ratio (95% CI) p-value	% ≥8 (95% CI)	GMT (95% CI) ^c	% ≥8 (95% CI)	GMT (95% CI) ^c	% diff ^b (95% CI) p-value	GMT ratio (95% CI) ^c p-value
1	99.0 (94.6, 100.0)	2.99 (2.54, 3.52)	100.0 (96.4, 100.0)	3.38 (2.95, 3.86)	−1.0 (−5.5, 2.8) 1.000	0.89 (0.72, 1.09) 0.255	93.8 (69.8, 99.8)	50.7 (24.9, 109.9)	84.6 (54.6, 98.1)	29.4 (13.9, 80.4)	9.1 (−19.8, 40.6) 0.573	1.72 (0.52, 5.16) 0.353
5	100.0 (96.4, 100.0)	2.09 (1.81, 2.41)	97.0 (91.5, 99.4)	1.74 (1.49, 2.03)	3.0 (−1.2, 8.4) 0.246	1.20 (0.97, 1.48) 0.087	95.0 (75.1, 99.9)	113.9 (65.9, 176.6)	95.0 (75.1, 99.9)	104.8 (57.2, 200.4)	0.0 (−22.4, 22.4) >0.99	1.09 (0.48, 2.34) 0.836
6A	79.0 (69.7, 86.5)	1.02 (0.79, 1.32)	91.0 (83.6, 95.8)	1.82 (1.48, 2.25)	−12.0 (−21.9, −2.0) 0.028	0.56 (0.40, 0.78) 0.001	100.0 (83.2, 100.0)	1243.9 (880.7, 1942.6)	100.0 (82.4, 100.0)	3068.2 (2052.7, 5700.0)		0.41 (0.23, 0.88) 0.007
6B	89.0 (81.2, 94.4)	1.57 (1.23, 2.00)	96.9 (91.1, 99.4)	3.64 (2.90, 4.59)	−7.9 (−15.8, −0.5) 0.049	0.43 (0.31, 0.60) <0.001	100.0 (82.4, 100.0)	1530.4 (821.7, 2516.2)	95.0 (75.1, 99.9)	2267.4 (950.0, 3873.7)	5.0 (−16.4, 26.9) >0.99	0.67 (0.32, 2.00) 0.380
7F	97.0 (91.5, 99.4)	2.19 (1.84, 2.61)	100.0 (96.4, 100.0)	3.88 (3.36, 4.49)	−3.0 (−8.4, 1.2) 0.246	0.56 (0.4, 0.7) <0.001	100.0 (83.2, 100.0)	876.6 (570.7, 1291.6)	100.0 (83.2, 100.0)	3763.2 (2562.5, 5702.5)		0.23 (0.13, 0.42) <0.001
9V	94.0 (87.4, 97.8)	1.07 (0.91, 1.26)	97.0 (91.5, 99.4)	2.19 (1.87, 2.56)	−3.0 (−9.8, 3.3) 0.498	0.49 (0.39, 0.61) <0.001	100.0 (83.2, 100.0)	197.2 (80.5, 379.5)	100.0 (83.2, 100.0)	752.8 (492.7, 1084.4)		0.26 (0.10, 0.57) <0.001
14	98.0 (93.0, 99.8)	4.96 (4.06, 6.07)	97.0 (91.4, 99.4)	4.47 (3.48, 5.76)	1.0 (−4.4, 6.7) 0.683	1.11 (0.81, 1.53) 0.523	100.0 (82.4, 100.0)	1243.4 (652.1, 2035.0)	94.7 (74.0, 99.9)	1108.0 (410.7, 2306.8)	5.3 (−16.2, 28.1) >0.99	1.12 (0.45, 3.48) 0.822
19A	92.0 (84.8, 96.5)	1.49 (1.22, 1.81)	97.9 (92.7, 99.8)	5.20 (4.22, 6.42)	−5.9 (−13.1, 0.6) 0.101	0.29 (0.21, 0.38) <0.001	94.1 (71.3, 99.9)	151.3 (51.7, 252.6)	100.0 (83.2, 100.0)	765.7 (568.6, 928.5)	−5.9 (−30.8, 14.9) 0.460	0.20 (0.07, 0.34) <0.001
19F	99.0 (94.6, 100.0)	3.87 (3.25, 4.62)	99.0 (94.6, 100.0)	5.38 (4.68, 6.19)	0.0 (−4.5, 4.6) 1.000	0.72 (0.58, 0.90) 0.004	100.0 (83.2, 100.0)	744.9 (580.7, 974.1)	95.0 (75.1, 99.9)	499.0 (223.8, 752.9)	5.0 (−15.6, 26.9) >0.99	1.49 (0.96, 3.77) 0.201
23F	91.0 (83.6, 95.8)	1.56 (1.28, 1.89)	91.0 (91.5, 99.4)	2.68 (2.21, 3.25)	−6.0 (−13.5, 0.9) 0.134	0.58 (0.44, 0.76) <0.001	100.0 (83.2, 100.0)	627.3 (294.4, 1040.3)	100.0 (83.2, 100.0)	921.4 (508.1, 1498.6)		0.68 (0.29, 1.47) 0.356

IgG GMC—immunoglobulin G geometric mean concentration; OPA GMT—opsonophagocytic assay geometric mean titer; CI—confidence interval.

^a Assays were conducted on a randomly selected subset.

^b Difference in treatment-group percentages SIIP-PCV – PCV13.

^c 95% CIs estimated from bootstrap resampling.

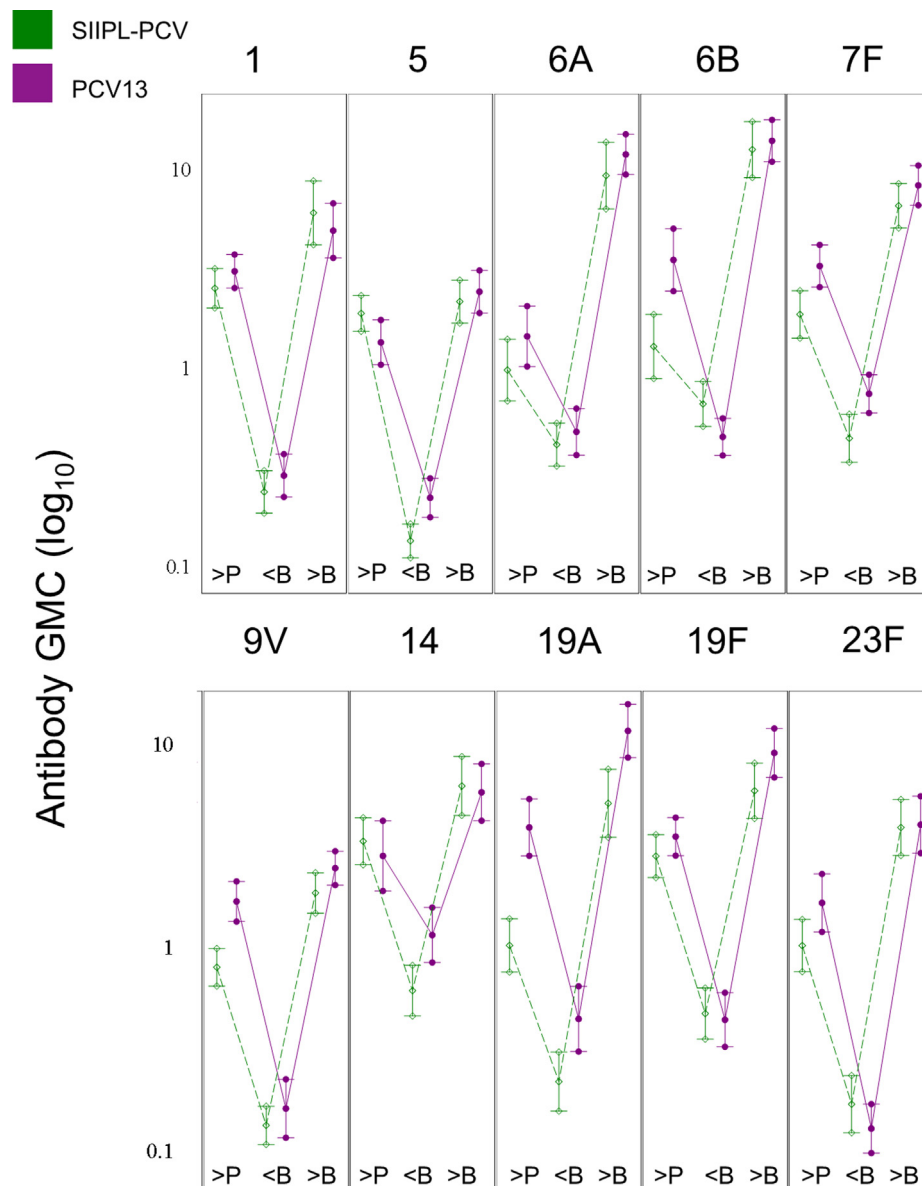


Fig. 3. Serotype-specific immunoglobulin G geometric mean concentrations (GMCs) post-primary series (>P), pre-booster (<B), 4 weeks post-booster (>B) with either SIIPL-PCV or PCV13 among infants contributing to booster phase (n = 96). Point estimates and 95% confidence intervals.

reflect chance events given an absence of consistent trends between age cohorts or across different vaccine doses in infants, reflecting the limited sample size of this phase 1/2 trial.

In the adult cohort, the IgG GMCs and OPA GMTs were consistently high four weeks after the administration of a single dose of either SIIPL-PCV or PPSV23. The responses to serotype 6A and 6B were higher following SIIPL-PCV and the response to serotype 1 was higher following PPSV23. The responses to other serotypes were comparable. Given the underlying biological differences in the nature of the immune responses to polysaccharide (PPSV23) and polysaccharide-conjugate vaccines (SIIPL-PCV) as well as the different quantities of polysaccharide antigens in the two vaccines, direct comparison of the serological responses they generate has some limitations [13,14,28,29]. Data on the protection conferred by PPSV23 in low-income settings are also limited [30–32]. Furthermore, nasopharyngeal pneumococcal carriage in The Gambia remains $\geq 50\%$ in adults of the age recruited to this trial and may impact not only natural, but also vaccine-induced serotype-specific pneumococcal immunity [33–36]. Nonetheless, the adult

data support further assessment of SIIPL-PCV although they should be interpreted with caution given the small number of subjects evaluated.

In PCV13-primed toddlers, a substantial booster response to all serotypes was observed in both treatment groups. The post-booster vaccination GMCs were comparable between groups. For three serotypes (5, 9V, and 19A) the magnitude of the booster response was greater following PCV13 than SIIPL-PCV although this in part reflected baseline GMCs, which tended to be higher in the SIIPL-PCV group. As in the adult cohort, the potential impact of differential past or concurrent nasopharyngeal carriage of given pneumococcal serotypes on the immune responses generated should be borne in mind given the limited sample size. Nasopharyngeal carriage of pneumococci in this age-group in The Gambia is in the region of 90%, including persistent vaccine-type carriage (e.g., 7F, 19F, and 23F) despite high PCV13 coverage [34,37]. In addition, the toddlers in this study had all received three priming doses of PCV13 as part of the Gambian EPI schedule. Few studies have examined the interchangeability of primary and booster

Table 6

Pneumococcal serotype-specific IgG GMCs four weeks after a booster dose of either SIPL-PCV or PCV13 and IgG GMC ratios (post-booster GMC/post-primary GMC) in the infant booster *per protocol* immunogenicity population.

	IgG GMC post boost			IgG GMC booster response		
	SIPL-PCV N = 48 GMC (95% CI)	PCV13 N = 47 GMC (95% CI) ^a	SIPL-PCV/ PCV13 GMC ratio (95% CI) p-value	SIPL-PCV N = 48 GMC ratio ^a (95% CI) ^b	PCV13 N = 47 GMC ratio ^a (95% CI) ^b	Ratio of GMC ratio (95% CI) p-value
1	6.24 (4.35, 8.94)	5.11 (3.76, 6.94)	1.22 (0.77, 1.95) 0.398	2.38 (1.80, 3.14)	1.58 (1.22, 2.04)	1.50 (1.04, 2.19) 0.033
5	2.30 (1.80, 2.93)	2.57 (2.02, 3.26)	0.90 (0.64, 1.25) 0.516	1.13 (0.87, 1.46)	1.77 (1.35, 2.30)	0.64 (0.44, 0.92) 0.016
6A	9.50 (6.53, 13.82)	12.06 (9.61, 15.12) ^e	0.79 (0.51, 1.22) 0.277	9.03 (5.92, 13.79)	7.75 (5.49, 10.94)	1.17 (0.68, 2.00) 0.574
6B	12.72 (9.29, 17.43)	14.06 (11.11, 17.79)	0.91 (0.61, 1.34) 0.611	9.01 (5.79, 14.03)	3.69 ^b (2.55, 5.33)	2.45 (1.38, 4.35) 0.003
7F	6.76 (5.26, 8.67)	8.51 (6.80, 10.65)	0.79 (0.57, 1.11) 0.172	3.43 (2.64, 4.46)	2.48 (1.92, 3.20)	1.38 (0.96, 1.98) 0.077
9V	2.44 (1.95, 3.07)	3.23 (2.67, 3.91)	0.76 (0.56, 1.01) 0.062	2.29 (1.80, 2.90)	1.46 (1.12, 1.89)	1.57 (1.11, 2.22) 0.012
14	8.16 (5.86, 11.38)	7.60 (5.52, 10.47)	1.07 (0.68, 1.69) 0.757	1.86 (1.38, 2.50)	2.05 (1.33, 3.15)	0.91 (0.54, 1.52) 0.710
19A	6.72 (4.57, 9.86)	15.20 (11.25, 20.54)	0.44 (0.27, 0.72) 0.001	4.83 (3.43, 6.81)	3.02 ^c (2.33, 3.90)	1.60 (1.05, 2.45) 0.030
19F	7.73 (5.66, 10.56)	11.85 ^e (8.99, 15.62)	0.65 (0.43, 0.99) 0.043	2.15 (1.56, 2.95)	2.61 ^d (1.96, 3.47)	0.82 (0.54, 1.26) 0.364
23F	5.11 (3.73, 7.01)	5.28 (3.83, 7.27)	0.97 (0.62, 1.51) 0.886	3.80 (2.80, 5.17)	2.42 (1.78, 3.27)	1.57 (1.03, 2.41) 0.037

IgG GMC – Immunoglobulin G geometric mean concentration.

^a IgG GMC post-booster/IgG GMC post-primary series for subjects with evaluable data at both time points.

^b N = 43.

^c N = 46.

^d N = 44.

^e N = 45.

PCV [38,39]. The responses to boosting with the licensed 10-valent PCV (Synflorix®, GlaxoSmithKline) following PCV13 priming have been shown to be generally lower than the responses to boosting with PCV13 [38]. These differences, however, may have been explained by the different carrier protein (*Haemophilus influenzae*-derived protein D) conjugated to the affected serotypes in the licensed 10-valent vaccine. Therefore, any role of the different priming vaccine in the somewhat lower responses to SIPL-PCV, which uses the same CRM₁₉₇ carrier as PCV13, is unclear.

Data from the infant cohort were intended to inform the decision to advance to a pivotal phase 3 trial designed to demonstrate that SIPL-PCV meets the product specifications required of a licensed and prequalified PCV as detailed in WHO guidance [40]. The guidance specifies that post-primary non-inferiority to a licensed PCV must be demonstrated, based on either seroresponse rates or IgG GMCs.

The seroresponse rates following a three-dose primary series of SIPL-PCV were above 90% for all except two serotypes. The point estimate for the difference in the seroresponse rates following SIPL-PCV compared to PCV13 was below the –10% non-inferiority margin used in previous PCV licensure trials for serotype 6A alone [20,21]. While generally higher in the PCV13 group, IgG GMCs following SIPL-PCV were above 1 µg/mL for all 10 serotypes, and the point estimate for the GMC ratio comparing SIPL-PCV with PCV13 was below the 0.5 non-inferiority margin used in previous

trials for only three serotypes (6B, 9V, and 19A) [20,21]. Furthermore, the percentage of subjects with functional OPA antibodies (titer ≥8) was above 93%, and was similar between the two groups, for all 10 serotypes. In particular, the immune responses to three serotypes (6B, 19F, and 23F) that were lower in the SIPL-PCV group based on IgG GMCs were similar between groups based on OPA GMTs. Data have suggested that OPA titers may ultimately correlate better with estimates of vaccine effectiveness than IgG concentrations, and high vaccine effectiveness has been demonstrated against disease endpoints despite generally lower IgG GMC than reported here [41–43]. Thus, while the responses generated following the SIPL-PCV primary series tended to be somewhat lower than those generated following the PCV13 primary series, they were considered to be robust with both vaccines. The effects of past or concurrent carriage should again be borne in mind although, given the double-blind, randomized design, are likely to become less important as the group size increases.

Comparing GMCs post-booster vaccination with the GMCs post-primary series, there was a booster response to all serotypes except serotype 5 following SIPL-PCV. The lack of booster response to serotype 5 reflected, at least in part, the relatively higher IgG GMC to this serotype in the SIPL-PCV group following the primary immunization series, as the post-booster IgG GMCs for this serotype were comparable between the SIPL-PCV and the PCV13 groups. Also, there was a substantial GMFR in antibody responses from

pre- to post-booster vaccination for all serotypes in both groups. While the IgG GMCs following the primary immunization series were higher for six serotypes following PCV13, these differences tended to be reduced or even reversed pre-booster, and additionally reduced post-booster. Only the IgG GMC to serotypes 19A and 19F remained higher in the PCV13 group post-booster. Serotype-specific differences between PCV13 and SIIP-PCV in the kinetics of the immune response have been observed between PCV13 and the licensed 10-valent vaccine in other studies and warrant further assessment [44]. These observations highlight the importance of assessing not only the primary response, but also antibody persistence and boosting as part of PCV evaluation.

The study has several important strengths. The integrated phase 1/2 age de-escalation design minimized logistical delay and ensured robust safety and immunogenicity data were generated in six-week-old infants to guide further vaccine development in a timely manner. The infant 6-, 10-, and 14-week schedule is in keeping with the requirements of the Target Product Profile for the Advanced Market Commitment for PCV, which sets out the specifications that new vaccines must meet to secure future purchase for Gavi-eligible countries [41]. The inclusion of an additional dose of the vaccine given between 10 and 14 months of age, and blood sample collected pre-booster, allowed both antibody persistence and booster response to be assessed. Furthermore, not only IgG but also functional antibodies were measured. The high *per protocol* follow-up and completion rates lend confidence in the results and ensured the maximum value of the study design was realized. Finally, reported differences in response to PCVs between high- and low-income countries, which may reflect differences in pneumococcal carriage rates or particular host factors [40], may limit the generalizability of studies conducted outside the target regions. Thus, undertaking the study in The Gambia, a low-income country in West Africa, ensures that the data are directly applicable to settings that stand to benefit from a vaccine such as SIIP-PCV in the future.

The study limitations are largely those inherent in any early-phase trial. The analysis is primarily descriptive. Where differences do exist, they should be interpreted with caution given there was no accounting for multiplicity. Similarly, the study was not sufficiently powered to confidently exclude differences between groups where these were not shown. The provisos present in the interpretation of the findings are as expected and will be addressed in future phase 3 trials.

5. Conclusions

The safety, tolerability and immunogenicity data generated support the future evaluation of SIIP-PCV in a phase 3, non-inferiority, licensure trial in infants.

6. Authors' contribution

SL, MRA, JF and EC contributed to trial design. EC and SL oversaw trial planning and implementation. AOB and MO contributed to and coordinated trial planning and implementation. AOB, MO, AU, MBH, IA and DG contributed to data collection. EC, SL, AOB, MO, AU, MBH, AT and BK contributed to study conduct. DHW analyzed the data. SL, EC, MRA, JF, DHW, RD and VS contributed to data interpretation. All authors provided input into the manuscript and approved the final manuscript.

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contained within are those of the authors and do not necessarily reflect positions or policies of the foundation.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: RD and VS are employees of SIIP. DG conducts contract and collaborative research with, and has advised vaccine manufacturers including GlaxoSmithKline, Merck, and Sanofi Pasteur. EC sits on a data safety monitoring board for Pfizer unrelated to pneumococcal vaccines. All other authors have no conflicts of interest to disclose.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2019.08.072>.

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